UPDATE ON MANAGEMENT OF CAROTID, AORTIC AND PERIPHERAL ARTERIAL PATHOLOGIES

Edited by
Michael Jacobs, MD
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UPDATE ON MANAGEMENT OF CAROTID, AORTIC AND PERIPHERAL ARTERIAL PATHOLOGIES

Edited by

MICHAEL JACOBS, MD, PHD
Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands
European Vascular Center Aachen-Maastricht, Germany and The Netherlands

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Törnqvist P., Dias N. V., Resch T.
Carotid artery revascularization by endarterectomy is an effective means of stroke prevention in selected patients with carotid stenosis. With the development of endovascular techniques, carotid artery stenting (CAS) has been proposed as a viable alternative to carotid endarterectomy (CEA), particularly in patients considered at high risk for CEA. Guidelines have established criteria that outline these patients who are considered at “high risk” for complications after CEA, to whom CAS may provide benefit. The validity of these theoretical high-risk criteria, however, is yet unproven, and, as a consequence, there is no clear evidence suggesting that the risk with CAS is lower in these high-risk patients compared with CEA. This manuscript summarizes the role of “high risk” within recent trials and discusses why the optimal treatment for these patients with deemed high risk for surgery remains a matter of debate.

**Key words:** Endarterectomy, carotid - Stroke - Risk assessment.

Carotid endarterectomy (CEA) has been established as the gold standard treatment for reducing the risk of stroke in patients with severe carotid artery stenosis and low to moderate operative risk. In those patients considered at high risk for complications after CEA, carotid artery stenting (CAS) has been proposed as the minimally invasive alternative. The definition of “high risk” generally includes those anatomic or clinical factors that increase the risk of complications with surgery, ranging from stroke to peripheral nerve injury. The concept of “high risk”, however, is dubious and may be interpreted in several ways; patients can be either at high risk for stroke or for periprocedural complications after CEA, or both.

The criteria that determine “high-risk” for CEA have been a matter of debate for a long time. Guidelines on the treatment of carotid artery disease have established criteria that outline these patients who are considered “high risk” for complications after CEA for whom CAS may provide benefit. These guidelines are based on the criteria first published in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, and these criteria have been used for inclusion and exclusion criteria in more recent randomized controlled trials comparing the outcome of carotid angioplasty and stenting with CEA (Table I). The SAPPHIRE population was chosen based on the desire to develop a less invasive but effective treatment for patients with a deemed high surgical risk, who account for up to one third of patients undergoing CEA. The validity of these theoretical high-risk criteria however are yet unproven. As a consequence, there is no clear evidence suggesting that the risk with CAS is lower in these high-risk patients compared with CEA. Therefore, the optimal treatment for these patients remains a matter of debate.

**The classic “high-risk” criteria**

Patients of older age, with previous radiation therapy or with restenosis after previous CEA have for
long been considered to be at high risk for (repeat) surgical intervention. Although older age has been clearly related to both a higher natural stroke risk as well as to a higher procedural risk, it should be clear that neither the operative risk for CEA nor the effectiveness of CAS has been proven in patients with a severe carotid restenosis or in patients with previous radiation therapy.

**Age**

There is a clear benefit from CEA in reducing the risk of ischemic stroke in patients with a recently symptomatic, significant carotid artery stenosis, particularly for patients >75 years, due to the relatively high risk for a secondary event and therefore a relatively low number needed to treat to prevent one ipsilateral stroke. Besides the favorable number needed to treat, overall life expectancy is increasing, indicating that CEA in the “intellectually intact” elderly can be highly beneficial. From observational studies, the periprocedural risk for the elderly undergoing CEA has been reported to be comparable to the risk for younger patients. Nevertheless, advanced age is thought to incur worse outcomes in those who undergo CAS, with octogenarians being the most vulnerable. In randomized trials, the relative harm of stenting strongly depended on age: risks of stroke or death in patients younger than 70 years old were similar in the two treatment groups; by contrast, there was a two-fold increase in the risk of stenting compared with endarterectomy among patients ≥70 years old. In the prespecified list of 16 subgroup variables, age was the only one that significantly altered the relative risk of stroke or death between stenting and endarterectomy in the short term. Possible mechanisms underlying this relationship may include increased burden of atherosclerosis, changes in plaque characteristics, or changes in vascular anatomy with increasing age, which may each increase the risk for thrombo-embolism during catheterization or stent deployment. Also, plaque vulnerability increases with carotid artery stenting.

### Radiation therapy

Patients with prior cervical radiation therapy (XRT) form a small but important subgroup of the potential patients considered for either CEA or CAS, because radiation therapy seems to accelerate the development of stenosis, leading to an increased risk of stroke. Previous XRT is one assumed anatomic risk factor, resulting in a “hostile” neck supposedly leading to technically more challenging surgery. Reported causative factors include absent tissue planes

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**Table I.—High risk in RCTs on CAS vs. CEA.**

<table>
<thead>
<tr>
<th>CMS</th>
<th>NASCET</th>
<th>SAPPHIRE</th>
<th>EVA3S</th>
<th>SPACE</th>
<th>ICSS</th>
<th>CREST</th>
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<tbody>
<tr>
<td>Age&gt;80</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>CHF</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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</tr>
<tr>
<td>Unstable angina</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>MI ≤30 days</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hemodialysis</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Contralateral occlusion</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Before after CABG</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Contralateral laryngeal NP</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Restenosis</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>High or low lesion</td>
<td>Y</td>
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<td>Y</td>
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<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Prior neck surgery</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Severe tandem lesion</td>
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<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
</tr>
<tr>
<td>Recent contralateral CEA</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
</tr>
<tr>
<td>Acute stroke ≤48 h</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
<td>excl</td>
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</tbody>
</table>

SAPPHIRE criteria have been uptaken by the Centers for Medicare and Medicaid Services (CMS) and have been used for inclusion and exclusion criteria in randomized controlled trials comparing CAS with CEA. However, this table shows that there is no unequivocal definition of high risk and the RCTs have each defined different criteria for exclusion and inclusion in their protocols (light grey=high risk criteria; dark grey=not uptaken as a high risk).
in the diseased vessel wall and poor tissue healing through radiation-induced fibrosis. Whether these arguments are sufficiently valid to consider a previously radiated patient as a high-risk patient for surgery is questionable.

In a systematic review of 27 articles comprising 533 patients undergoing XRT (361 CAS and 172 CEA) the pooled analysis showed a perioperative risk for “any cerebrovascular adverse event” (CVE) of 3.9% (95% CI, 2.3-6.7%) in CAS against 3.5% (95% CI, 1.5-8%) in CEA (p=0.77). Risk for temporary cranial nerve injury (CNI) after CEA was 9.2% (95% CI, 3.7-21.1%) versus none after CAS. Late outcome showed rates of CVE favoring CEA (p=0.014) with an estimated rate of 4.9 per 100 person-years (95% CI, 3.6-6.6). Restenosis rates were significantly higher in patients undergoing XRT than in other deemed high-risk subgroups. Comparison of outcomes for restenosis and/or occlusion showed a significant difference favoring CEA (p=0.003). However, most in-stent restenoses behaved in a benign fashion and remained asymptomatic. The underlying mechanism leading to in-stent restenosis after CAS is explained by myointimal hyperplasia with smooth muscle cell proliferation. Stent deployment in a pre-existent fibrotic (postradiation) process may be associated with a faster and higher incidence of restenosis.

**Restenosis after ipsilateral CEA**

Restenosis after surgery hampers the long-term durability of CEA in terms of stroke-free survival. The optimal treatment strategy of significant restenotic lesions remains unclear. Redo-CEA potentially leads to a more challenging surgical procedure, and therefore restenosis following prior CEA has been adapted among the “high-risk” criteria.

While a randomized control trial is not feasible, a recent meta-analysis of individual patient data showed that in symptomatic and asymptomatic patients with restenosis after prior ipsilateral CEA, CAS was not superior to CEA regarding perioperative stroke and death rate or restenosis rate during follow-up. In total, 13 studies were included, contributing to 1132 unique patients treated by CAS (10 studies, N. = 653) or CEA (7 studies; N. = 479). After adjusting for potential confounders, the primary endpoint (death or stroke) did not differ between CAS and CEA groups (2.3% vs. 2.7%, adjusted odds ratio [OR] 0.8, 95% CI: 0.4-1.8). Also, the risk of restenosis during a median follow-up at 13 months was similar for both groups (hazard ratio [HR] 1.4, 95% CI: 0.9-2.2). Transient cranial nerve injury (CNI) was reported in 5.5% of CEA patients.

These results indicate that the restenosis criterion should not be used to preferentially treat these patients with CAS. As a consequence, both CAS and CEA seem suitable options to treat restenosis after prior ipsilateral CEA. Although CEA may be counterbalanced by a risk for transient CNI, CAS is limited by access site complications and technical failure. However, it should be reaffirmed that permanent CNI can be a serious and debilitating complication limiting the benefit of carotid surgery in preventing stroke. The risk of CNI should be taken into account at all times when selecting optimal treatment for patients with restenosis after prior CEA.

**High-risk criteria in recent RCTs on CAS versus CEA**

SAPPHIRE criteria have been used to define inclusion and exclusion criteria in recent randomized controlled trials comparing CAS with CEA. However, there is no unequivocal definition of high risk and the RCTs have each defined different criteria for exclusion and inclusion in their protocols (Table I). The Stent-Protected Angioplasty vs. Carotid Endarterectomy (SPACE) trial randomized 1183 symptomatic patients and excluded patients with restenosis and previous radiation. No other risk status restrictions were instituted; however, some high-risk patients were probably excluded under the criterion of severe concomitant disease with poor prognosis, as determined by individual physicians. The results showed no differences in outcomes of stroke/death between CAS and CEA at 30 days, yet failed to prove non-inferiority of carotid stents.

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anatomically not suitable for surgery were excluded from the study.

The Carotid Revascularization Endarterectomy vs Stent Trial (CREST) randomized 2502 patients, 52% of whom were symptomatic. Patients were mostly not at high risk because the study excluded patients with all major high-risk criteria as set by CMS except age >80 years and contralateral internal carotid artery occlusion. The low event rates in CREST may be explained somewhat by the fact that most patients were “low risk.”

The SAPPHIRE trial is known as the first and only trial to evaluate patients with a deemed high risk for surgery and showed non-inferiority of CAS compared with CEA in the high-risk population. However, the patients were not stratified by symptom status, and >70% were asymptomatic. The subsequent SAPPHIRE registry data showed that patients with physiologic high-risk factors had an increased risk of 30-day adverse events compared with patients with anatomic high-risk factors (4.9% vs. 2.8%; P=0.0306).

Population based studies on deemed high-risk criteria

The current Center for Medicare and Medicaid Services (CMS) guidelines include symptom status, degree of stenosis, specific physiologic or anatomic risk factors deemed high risk for CEA. The CMS physiologic high-risk criteria, based on the criteria first published in the SAPPHIRE trial, are intended to identify patients who are at increased risk for complications with CEA. Physiologic high-risk variables include age >80 years, New York Heart Association class III congestive heart failure, left ventricular ejection fraction <30%, unstable angina, myocardial infarction (MI) ≤30 days, contralateral internal carotid artery occlusion, recent coronary artery bypass grafting (CABG) or valve repair, and hemodialysis. Anatomic high-risk factors include contralateral laryngeal nerve palsy, restenosis, history of neck radiation, high or low lesion, and prior neck surgery.

A recent analysis revealed that a physiologic high-risk status was associated with increased stroke or death, whereas anatomic high-risk status showed a trend toward increased stroke or death in symptomatic patients undergoing CAS compared with non-high-risk patients undergoing CAS or physiologically high-risk patients undergoing CEA. In total 271 CAS and 830 CEA patients were studied. Among the symptomatic patients, physiologic high-risk status was associated with increased stroke/death (14.3% vs. 2.7%; P<0.01) in patients who underwent CAS compared with CEA. Symptomatic, anatomic high-risk patients showed a trend toward higher rates of stroke (12.9% vs. 0%; P=0.15) and stroke/death (16.1% vs. 0%; P=0.14) after CAS.

This analysis revealed two important findings. First, significantly higher rates of stroke or death were observed in physiologically high-risk symptomatic patients after CAS than after CEA. Second, an increased risk of stroke or death was observed in physiologically high-risk symptomatic patients compared with non-high-risk symptomatic patients undergoing CAS, but this was not observed in patients undergoing CEA. In summary, among symptomatic patients, those who are physiologically at high risk may have the highest risk of 30-day adverse events after CAS.

In a further CMS based analysis on 10,107 patients undergoing CEA (6370) and CAS (3737), stratified by CMS high-risk criteria, the primary endpoint was composite death, stroke, and MI (major adverse cardiovascular event [MACE] = composite of death, stroke, and MI) at 30 days. CAS had higher rates than CEA for MACE (OR 1.2; 95% CI, 1-1.5), death (OR, 1.5; 95% CI, 1-2.2), and stroke (OR, 1.3; 95% CI, 1-1.7), whereas there was no difference in MI (OR, 0.8; 95% CI, 0.6-1.3). Among CEA patients, age ≥80 (OR, 1.4; 95% CI, 1.02-1.8), congestive heart failure (OR, 1.7; 95% CI, 1.03-2.8), EF <30% (OR, 3.5; 95% CI, 1.6-7.7), angina (OR, 3.9; 95% CI, 1.6-9.9), contralateral occlusion (OR, 3.2; 95% CI, 2.1-4.7), and high anatomical lesion (OR, 2.7; 95% CI, 1.33-5.6) predicted MACE. Among CAS patients, recent MI (OR, 3.2; 95% CI, 1.5-7) was predictive, and radiation (OR, 0.6; 95% CI, 0.4-0.8) and restenosis (OR, 0.5; 95% CI, 0.3-0.96) were protective for MACE.

Although CMS high-risk criteria can successfully discriminate a group of patients at high risk for adverse events after CEA, certain CMS high-risk criteria are more important than others. However, CEA appears safer for the majority of patients with carotid disease. Among patients undergoing CAS, non-high-risk status may be limited to restenosis and radiation. Considering anatomic high-risk factors, patients with contralateral occlusion were at high risk for adverse...